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THE SAFE AND ECONOMICAL CARE OF Ta BLADDER CANCER

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ABSTRACT

Introduction: Stage Ta bladder cancer (TaBC) accounts for around half of all new cases of urothelial bladder cancer (UBC), and displays a heterogeneous behavior with 5 yr recurrence rates which vary from 31% to 78%, whilst progression ranges from 0.8% to 45%. Optimal management is crucial to achieve safe yet economical long-term outcomes. The purpose of this paper is to provide an overview of such management.

Methods: Using American Urological Association, **National Comprehensive Cancer Network (NCCN)**, European Association of Urology (EAU) and the International Consultation on Urological Diseases-EAU (ICUD-EAU) guidelines as the basis of this non-systematic review, we utilized *PubMed* searches to update the literature in this field, and to expand upon topics of particular interest or controversy.

Results: We have provided an overview for the practicing urologist of the safe and economical care of TaBC with regard to risk stratification, pre- and peri-operative care, subsequent adjuvant treatment, surveillance, management of recurrences and long-term outcomes. Whilst these recommendations are already incorporated within current guidelines, some aspects deserve further discussion or have been the subject of relevant research subsequent to guideline publication.

Conclusions: The traditional view that TaBC is invariably synonymous with low risk disease requires re-evaluation. Modern management of TaBC depends on initial risk stratification that allows subsequent management based on a number of evidence-based guidelines. Given the

usual long clinical course of TaBC, such an approach ensures not only safe but economical care of this group of patients.

INTRODUCTION

Urothelial bladder cancer (UBC) is the fifth most common cancer in Western societies, accounting for 69,000 and 180,000 new cases per year in the USA and EU [1], respectively. Emerging patterns of cigarette smoking and occupational carcinogen exposure mean that the incidence of UBC is rising globally [2]. However, there has been little improvement in the outcome for patients with UBC since the 1980s [3,4], possibly reflecting complex patient pathways and treatments, combined with a lack of therapeutic advances [4].

As a result of the chronic clinical course of non-muscle-invasive bladder cancer (NMIBC), its prevalence relative to muscle-invasive disease (MIBC), and the risks of recurrence and progression that necessitate long-term cystoscopic surveillance and frequent interventions, the associated cumulative costs of NMIBC are considered to be greater than those for MIBC [5, 6]. It is also evident that the care for patients with NMIBC cancer varies considerably **both by region [7] and by physician [8]. Indeed, the latter has been shown to have more influence over the cost of NMIBC care than the stage and grade of the disease itself [9]**.

Stage Ta bladder cancer (TaBC) is defined as a non-invasive papillary carcinoma of the bladder[10] and accounts for 48-53% of all new cases of UBC [11,12], a proportion that has remained stable for 20 years [11,13]. TaBC displays a heterogeneous behavior with 5 yr recurrence rates which vary from 31% for a solitary <3cm G1pTa to 78% for a recurrent > 3cm multifocal G3pTa with carcinoma in situ (CIS), whilst progression for the same tumours ranges from 0.8% to 45%, respectively [10]. Although conventionally patients with TaBC have been labeled as 'low-risk' non-

muscle invasive bladder cancer (LR NMIBC), 30% have high grade or G3 disease [13] and over 11% of patients will progress and may eventually die from bladder cancer [14,15]. There is therefore a need to stratify TaBC patients for optimal management.

The aim of this review is to provide an overview of the safe and economical management of patients with TaBC, and based upon a validated risk stratification scheme such as that proposed by the EAU Guidelines on NMIBC [10].

METHODS

This is a non-systematic review specifically focusing on issues relating to TaBC. AUA, **NCCN**, EAU and ICUD-EAU guidelines were reviewed [16,17,18], along with papers obtained following *PubMed* searches of relevant search terms to take account of more recent evidence in this field. These were used by the authors, in conjunction with their consensus opinion as experienced urologists, to produce a review of the safe and economical care of TaBC. **Detailed economic assessments of UBC practice have been undertaken recently, exemplified by [6] and [19], and have been incorporated into our consensus opinion; recapitulating such analyses was considered to be beyond the scope of this review, especially given their significant geographical variation as illustrated in Table 1.**

DEFINING NMIBC RISK CATEGORIES

In 2006 The European Organisation for Research and Treatment of Cancer (EORTC) published risk tables to predict recurrence and progression in individual patients based on an algorithm utilising a number of clinical and pathological factors: tumor number, tumor size, prior recurrence rate, T stage, presence or absence of CIS, and grade [20]. The tables were based on an analysis of data from historical trials, although other studies have suggested that when used as part of modern NMIBC management they overestimate recurrence and progression [21]. However, to date, there is no better risk categorization tool.

Originally intended to be used as an aid to discussing treatment options with patients, they were subsequently used by the EAU NMIBC guidelines committee as the basis for their recommendation to categorize NMIBC into low, intermediate and high risk [10]:

- Low-risk tumors: Primary, solitary, Ta, low grade/G1, <3 cm, no CIS.
- High-risk tumors: Any of the following - T1 tumor, high grade/G3 tumor, CIS and specifically recurrent multiple >3 cm Ta G1/2 tumors
- Intermediate-risk tumors: All other tumours

Although the concept of high-risk NMIBC has been in use for some time, it is no longer appropriate to consider all other NMIBCs as a single homogeneous group and the use of risk categorization should be considered an essential first step in the safe management of all TaBC. In addition, there is a need to recognise a state of progression prior to muscle-invasion

such that a tumor's behavior can be appropriately characterized and managed. Therefore, the concept of 'biological progression' has recently been defined by the International Bladder Cancer Group as: an increase in T stage from CIS or Ta to T1, development of T2 or greater or lymph node (N+) disease or distant metastasis (M1), or an increase in grade from low to high [22].

PRE-OPERATIVE CARE

Urine Cytology and Urinary Markers

Following initial identification of a papillary bladder tumor, additional urine cytology and urinary markers are of limited value in the preoperative management of TaBC [18] since they are unlikely to alter subsequent surgical management. However, they may have an important role during follow-up, as discussed below.

Upper Tract Studies

The incidence of synchronous upper tract urothelial carcinoma (UTUC) is unclear but is likely to be low since the incidence of metachronous UTUC in TaBC is very low (0.3%) [23]. Nevertheless it has been suggested that multifocal NMIBC carries a higher risk of UTUC [24]. All patients with UBC should have an ultrasound of the urinary tract as part of their initial investigations which is sufficient to identify significant upper tract disease such as renal cell carcinoma, stones and UTUC. Further imaging with computed tomography, magnetic resonance imaging or intravenous urogram in patients with TaBC specifically to identify synchronous UTUC carries additional risks and is not recommended [18].

PERI-OPERATIVE CARE

Transurethral Resection

The initial gold standard treatment of any suspected bladder tumor remains transurethral resection (TURBT) in order to allow complete removal and histological classification of the tumor including assessment of the depth of invasion [25]. There is increasing evidence that the quality of the TURBT has a major impact on the recurrence rate [26] and that experienced urologists have lower recurrence rates than trainees [27]. There has been recent interest in the use of visual aids at the time of TURBT such as blue light photodynamic diagnosis (PDD) or narrow band imaging (NBI). **Two recent meta-analyses have confirmed a 20% increased tumour detection rate for PDD over white light cystoscopy alone [19,28], with the inference that detecting as many tumors as possible at the time of initial TURBT reduces the recurrence rate at the first check cystoscopy . However, despite an improved initial detection rate, this has not translated into improvements in long-term recurrence rates when compared to white light [29]. Therefore, at the present time, there is no compelling evidence that using PDD or NBI results in better outcomes for patients with TaBC.**

Immediate Intravesical Chemotherapy

A single dose of intravesical chemotherapy (IVT) within 24 hours of TURBT has been shown to reduce the odds of recurrence by 39% [30]. Although recent studies have questioned the value of

such a policy for all patients, the value of preventing small recurrences has been confirmed [31]. Since even the most favorable prognosis TaBC patients will have a 5 year recurrence rate of 31%, and whilst a study has shown 93% correlation between a visual diagnosis of a Ta tumor and histology [32], it would seem reasonable to offer all patients with apparent TaBC a single instillation of IVT at first presentation. Unfortunately, according to a recent survey, the uptake of a single instillation of IVT is low in the US with only 16.9% of eligible patients receiving IVT, whilst 66% of those surveyed never offered it [33]. One barrier to more widespread adoption of immediate peri-operative IVT may be the difficulties of ensuring timely instillation by appropriately trained personnel in operating theatres or wards. This may be overcome by administration of the IVT by the operating urologist at the end of TURBT, which is considered safe [34].

FURTHER MANAGEMENT

Early Re-Staging TURBT

All patients with high-risk TaBC should undergo an early re-staging TURBT within 4-6 weeks - this has been shown to identify and remove residual tumour as well ensuring that understaging of MIBC has not occurred [17,18,35,36]. In low-risk TaBC, a re-staging TURBT should only be considered when there is doubt about the completeness of the original TURBT [10].

Adjuvant Intravesical therapy

The need for further adjuvant therapy in patients with TaBC will depend on their stratification as low-, intermediate or high-risk Ta tumors **as defined above by the EAU** [10].

Low-risk Ta

These tumors make up 50-70% of all TaBCs [13]. Apart from a single instillation of IVT immediately following TURBT, as discussed above, no further adjuvant treatment is indicated in this group [10,17,18].

High-risk Ta

These tumors make up 20-30% of all TaBCs [13]. Such patients require an induction course of BCG followed by a minimum of 1-3 years of maintenance BCG in order to reduce the risk of recurrence [10]. The effect of BCG on progression is less clear [18,37].

Intermediate-risk Ta

The EAU guidelines alone describe these as a separate and distinct group. In order to reduce the risk of recurrence the EAU guidelines recommend one immediate instillation of IVT followed by 1 year full-dose BCG treatment, or by further instillation of IVT for a maximum of 1 year [10].

SURVEILLANCE

Cystoscopy

In order to mitigate the risks of recurrence and progression described above, the safe long-term management of TaBC is founded upon diligent cystoscopic surveillance. The first cystoscopy after TURBT at 3 months is considered a key prognostic indicator for recurrence and progression [38]. For subsequent surveillance the EAU, NCCN and AUA guidelines show disparity, with the NCCN and AUA guidelines being less specific [6]. The EAU guidelines take a risk-adapted approach [10]:

- For patients with low-risk tumors, the first surveillance cystoscopy should take place 3 months following TURBT; if negative, the next cystoscopy should take place 9 months later, with surveillance continuing for 5 years.

- Patients with high-risk tumors should undergo cystoscopy and cytology at 3 months following TURBT. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for 2 years, every 6 months thereafter until 5 years, and then yearly.

- Patients with intermediate-risk tumors should have an in-between follow-up scheme using cystoscopy and cytology, adapted according to personal and subjective factors.

- In tumors originally intermediate- or high-risk, recurrences after 10 years tumor-free interval are not unusual. Therefore, lifelong follow-up is recommended.

NCCN guidelines state that patients with Ta low-grade tumors should *"undergo a cystoscopy at 3 months initially, and then at increasing intervals",* whilst Ta high-grade tumors should be followed up *"with a urinary cytology and cystoscopy at 3-6 month intervals for the first 2 years, and at increasing intervals as appropriate thereafter"* [17]. The AUA guidelines state that: *"Although a variety of different follow-up strategies have been advocated, the most common approach has included patient assessment every three months in the first two years after initial diagnosis followed by every six months for the subsequent 2 to 3 years, and then annually thereafter. Clinical follow-up involves an appropriate patient history including voiding symptoms and hematuria, urinalysis, cystoscopy, and urine cytology"* [16].

Evidence in support of the risk-adapted approach originates over 20 years ago with economic benefits demonstrated [39]. To our knowledge, formal health economic evaluations or randomized studies of varying schedules of surveillance have not been carried out since [10]. **Other aspects regarding the safe and economical management of TaBC require further discussion**. Firstly, the EAU guidelines recommend a surveillance period of 5 years for low-risk NMIBCs if no recurrences are detected during surveillance [10]. Given the long-term outcomes described above for TaBC, with a meaningful risk of death from bladder cancer, we suggest that surveillance should continue for at least 10 years for low-risk TaBC; other authors have recently made similar recommendations [15]. Secondly, variation in treatment intensity does not impact survival or the avoidance of subsequent major interventions [9], **so more intensive surveillance schedules than recommended should be avoided**. However, the influence of *"personal and*

196 *subjective factors"* on NMIBC surveillance should not be underestimated [10]. Despite the
197 evidence-based guidelines above, clinicians know their patients best - all who work in this field
198 appreciate the 'feel' that one gets for the behavior of a particular patient's tumor during the
199 course of years of surveillance. It is therefore difficult to criticize any urologist taking a
200 personalized approach on a case-by-case basis, and especially in younger patients with a life-
201 expectancy of over 30 years. However, given these caveats, we feel that the risk-adapted
202 approach of the EAU guidelines represents the most appropriate approach to NMIBC
203 surveillance, and intuitively results in a cost benefit [6].

204

205 **Upper Tract Surveillance**

206 The EAU guidelines recommend annual upper tract imaging with CTU or IVU for patients with
207 high-risk tumors, or if cytology is positive in the absence of visible tumour [10], whilst the AUA
208 guidelines state that: *"Surveillance often includes periodic upper tract imaging, especially for*
209 *high-risk patients"* [16]. However, the supporting evidence for such an approach for patients with
210 TaBC is unclear. Sternberg et al retrospectively reviewed the treatment and follow-up of 935
211 NMIBC patients, from which 51 patients were subsequently diagnosed with UTUCs with a
212 median follow-up of 5.5 years [40]. The 5- and 10-year UTUC-free probabilities among patients
213 with Ta tumors were 98% and 94% respectively [40]. During the follow-up period, UTUC was
214 diagnosed in 16 out of 481 patients with Ta NMIBC (3.3%): 10 (2.1%) after symptoms developed
215 and only 4 (0.8%) on routine imaging (2 unknown, 0.4%) [40]. The authors concluded that: *"While*

upper tract recurrence remains a lifelong risk for patients with bladder cancer, only a minority will be diagnosed on routine surveillance CT urography. The majority of UTUC can be diagnosed with a surveillance strategy including thorough history, physical examination, urine cytology, cystoscopy and renal sonography" [40]. An optimal upper tract surveillance schedule is therefore yet to be defined for patients with TaBC, and further studies are needed.

Cytology and Urinary Biomarkers

Urine cytology is subjective and expensive, with low sensitivity (10-51%) yet high specificity (83-96%) [19,41]; it is this high specificity which makes it an attractive test. However, its role in the surveillance of low-risk Ta tumors has to be questioned, despite having an important role in the surveillance of intermediate- and high-risk Ta tumors [10].

Accurate urinary biomarkers could theroretically reduce the frequency of cystoscopy for low- and intermediate-risk groups, thus reducing patient burden, improving quality of life, and reducing costs to healthcare providers. For patients with high-risk disease, urinary biomarkers could be utilized in-between surveillance cystoscopies, with positive results prompting rigid cystoscopy±TURBT, potentially reducing the risk of progression to MIBC during surveillance. Although a number of biomarkers are commercially available and FDA-approved, no single marker or test has yet demonstrated sufficient sensitivity and specificity to be acceptable to patients and clinicians, and to replace cystoscopy [19,42]. For these reasons, the AUA guidelines

conclude that: *"At the present time, the use and utility of urine-based molecular markers in the follow-up of patients remains uncertain"* [16], and the EAU guidelines that: *"No non-invasive method has been proposed that can replace endoscopy, therefore, follow-up is based on regular cystoscopy"* [10].

MANAGEMENT OF RECURRENCES

Office Fulguration and TURBT

Conventionally, recurrences are managed by TURBT in the operating theatre. Tumour is obtained for histopathological examination alongside biopsy material from any abnormal or suspicious areas of the urothelium. This represents the safest and most appropriate management of patients with intermediate- and high-risk TaBC.

Whilst the absence of detrusor muscle (DM) in the resection specimen is associated with a higher incidence of residual disease and early recurrence, many recurrent TaBCs are small papillary lesions that are unlikely to involve the lamina propria and DM. In such cases a further deeper resection than needed to remove the tumor itself, simply to obtain DM, is unnecessary[25,18].

In many patients with recurrent low-risk TaBC, inpatient TURBT under general or regional anaesthesia may represent overtreatment. It is considered that these patients can be safely managed by fulguration/ablation in the office setting [43,44]. This view is supported by the EAU guidelines which state: "*Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden"* [10]. **However, the benefits of convenience and reduced cost and burden to the patient and clinician should be carefully considered against the risks of not undertaking histopathological examination of the lesion and potentially missing grade or stage progression.** The balance of risk depends upon the

experience of the clinician and their ability to correctly identify low-risk TaBC macroscopically. Published data demonstrates that clinicians with a specialized bladder cancer interest can correctly prediction G1 pTa recurrences in 93-99% of patients [32], **but outside of such settings the results are less favourable [45]. We are therefore of the opinion that for the safe management of TaBC, office fulguration/ablation alone (without biopsy) may be an unsuitable approach for urologists without a specialized bladder cancer practice**. Clearly, common sense should prevail, and office/outpatient fulguration/ablation may have wider applicability for very elderly or infirm patients with comorbidities.

Active Surveillance

The terms active surveillance (AS), observation, expectant management and watchful waiting are all used to describe cystoscopic monitoring of Ta recurrences. In specialized practices TaBC recurrences can be identified accurately in 93% of cases rising to 99% if urine cytology is also used [32]. Their natural history is well known and is characterized by recurrences requiring repeated treatment, rather than by progression. The concept of AS was first described by Soloway [46] who observed progression in either stage or grade in 9% of TaBCs, whilst no patients developed MIBC. These findings have been confirmed by others [47,48], with grade progression ranging between 9-16% and stage progression ranging between 4.5-6%. AS requires a clear discussion between urologist and patient and may be particularly suitable for patients with significant comorbidity. Finally, AS lends itself to combination with office fulguration, and a

combination of approaches using AS with office biopsy and fulguration of recurrences, followed by an immediate instillation of IVT, may allow many TaBC patients to avoid inpatient TURBT (MS Soloway, personal communication) [18].

Chemoresection in the Treatment of NMIBC

Several small studies have shown promising results with complete ablation of small papillary tumours with intravesical chemotherapy alone (chemoresection), but the optimal schedule and the effectiveness of chemoresection for TaBC is unclear [49]. Two reviews of chemoresection included over 1,200 patients in all three NMIBC risk groups and described a number of different chemotherapy agents given in 4-8 instillations. On average, complete response was 50%, with therapeutic effect sustained for at least 2 years [49,50]. The National Institute of Health Research (UK) have recently funded a randomised trial of chemoresection versus standard surgical management of low-risk NMIBC (CALIBER trial) which should help define the role of chemoresection in TaBC.

LONG-TERM OUTCOMES

The long-term outcome from TaBC is worthy of particular mention. Wallace et al demonstrated that, when followed-up for over 8 years, 21% of patients who subsequently died following an initial diagnosis of TaBC were certified to have died from bladder cancer [14]. Although this cohort of patients was recruited in 1991-2 (and treated according to UK practice at the time), these data would suggest that TaBC is perhaps a more significant disease in the long-term than generally considered. The ongoing follow-up of this cohort of patients (now over 18 years) substantiates this supposition (RT Bryan, unpublished data).

DISCUSSION

The AUA, **NCCN**, EAU and ICUD-EAU guidelines are excellent documents providing essential advice for the management of NMIBC [10,16,17,18], and are regularly and thoroughly updated by experts in the field. They therefore represent safe practice for the management of TaBC, and we have used these guidelines as the basis for this review. However, some aspects deserve further discussion or have been the subject of relevant research subsequent to guideline publication. In conjunction with our consensus opinion as experienced urologists in this field **and whilst incorporating data from economic analyses [6,19]**, we have written this paper as a review of the safe and economical care of TaBC that is of most relevance to a clinical urological readership. This approach is summarized in **Figure 1**.

The non-medical costs that are associated with UBC care, costs that are borne by patients, their families, and their employers, are huge [6], and there is a plethora of further research that is urgently required in this setting [4,6]. For example, in the current era of enhanced optical modalities for cystoscopy it is feasible that a technology with increased sensitivity for detecting recurrences (such as NBI) may permit the intervals between surveillance cystoscopies to be lengthened for low- and intermediate-risk NMIBCs. Such approaches would clearly lead to economic benefits and reduced patient burden if equivalent outcomes to conventional surveillance schedules could be maintained; randomized studies comparing the various enhanced optical modalities are therefore urgently required. Similarly, CTU may permit upper tract surveillance intervals to be increased in some groups of patients, and further studies are

also needed [40]. Furthermore, although existing commercial and FDA-approved urinary biomarkers do not have real clinical utility due to their relatively low sensitivities and specificities, the latest generation of research platforms show significant promise in the field of urinary biomarker discovery.

Chemoprevention of NMIBC recurrence is a topic that remains outside the scope of current guidelines, although a number of such trials are currently in follow-up (e.g. BOXIT, SELENIB). Likewise, chemohyperthermia and electromotive drug administration may become important tools in the urologist's armamentarium in the future.

Office fulguration/ablation is not widely practiced by European urologists despite favourable evidence from the USA (probably due to provider/practice differences), although the technique appears safe, convenient and cost-effective [43,44]. However, without biopsying the lesion beforehand we do not feel that we can recommend this as a universal approach to the management of recurrent tumors in patients previously/consistently diagnosed with low-risk TaBC outside of specialized bladder cancer practices, or unless determined by the frailty of the patient. Furthermore, in an era where genetic and epigenetic analyses on nanogram amounts of DNA are likely to yield considerable prognostic information, the importance of biopsy material is likely to appreciate significantly. Omission of a simple biopsy is thus likely to become an increasingly inappropriate approach in the cancer setting.

CONCLUSIONS

The traditional view that TaBC invariably represents low-risk disease requires re-evaluation: a significant number of patients will progress, and a number will die from their disease. Modern management of TaBC depends on initial risk stratification that allows subsequent management to be based on a number of evidence-based guidelines. Given the usually long clinical course for most patients with TaBC, patients often suffer many recurrences and are subjected to repeated surgical intervention. An evidence-based approach ensures not only safe but economical care of this group of patients.

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LEGEND FOR TABLES

Table 1

The costs of bladder cancer care, shown in Euros (taken from Svatek et al [6] with permission). BCG = bacillus Calmette-Guérin; MMC = mitomycin C; TURBT = transurethral resection of bladder tumour. *US Medicare rates.

LEGEND FOR FIGURES

Figure 1

A flow-chart representing the management of NMIBC, demonstrating the differences between the AUA and EAU guidelines (w=weeks, m=months, y=years, CTU=CT urography) [10,16]. Our views and interpretations are included in the dashed boxes.

493 **Table 1:**

494

	United States*	United Kingdom	Sweden	Germany	Italy
Office cystoscopy	163	520	165	-	-
TURBT	4348	2362	2200	2500	2242
Single dose of MMC 40mg	219	87	-	-	-
BCG 6 weeks	528	630	-	-	975
Cystectomy	23451	8090	20570	15419	7222

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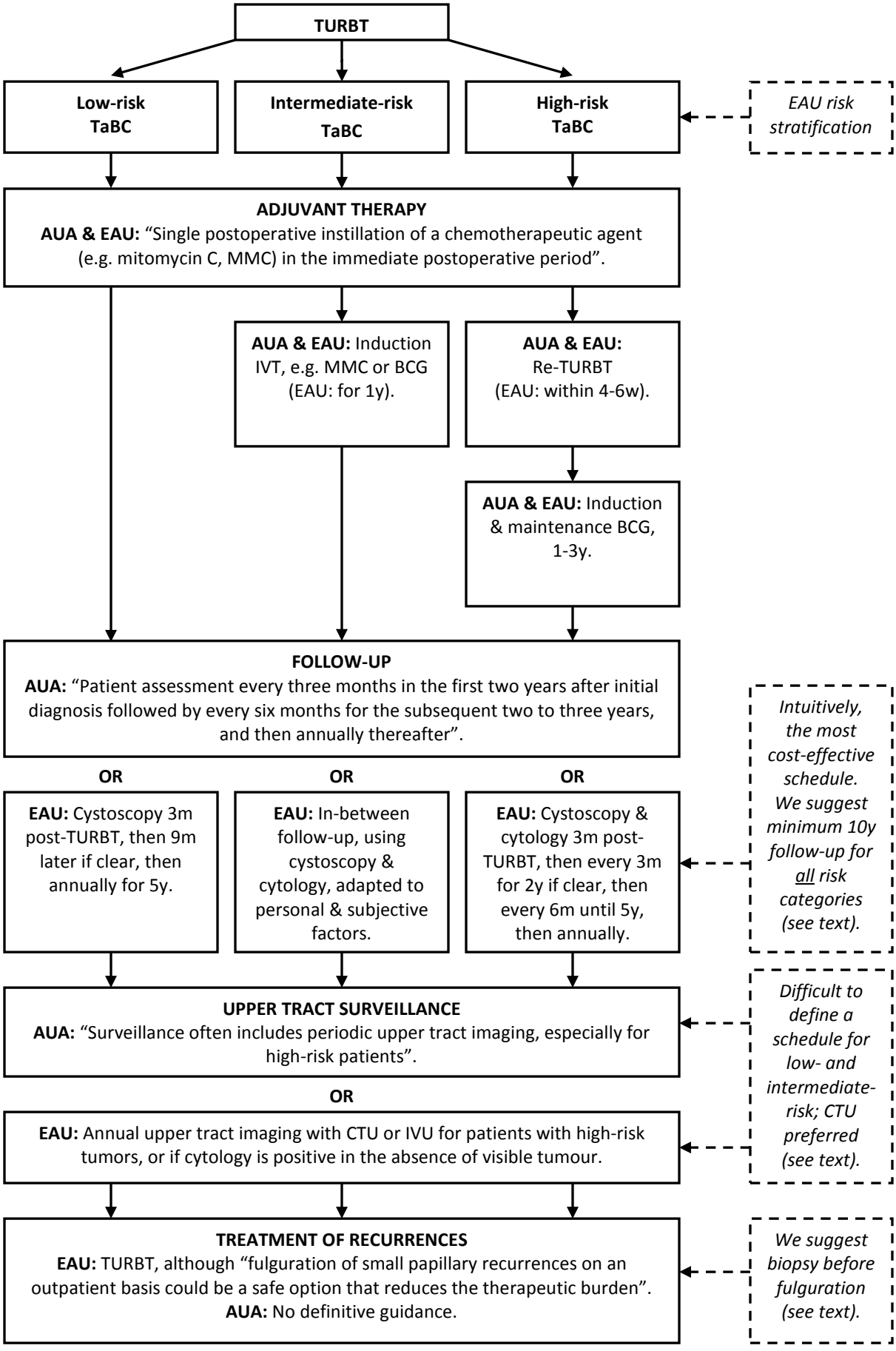
Figure 1:


TURBT
Low-risk TaBC
Intermediate-risk TaBC
High-risk TaBC
EAU risk stratification
ADJUVANT THERAPY
AUA & EAU: "Single postoperative instillation of a chemotherapeutic agent (e.g. mitomycin C, MMC) in the immediate postoperative period".
AUA & EAU: Induction IVT, e.g. MMC or BCG (EAU: for 1y).
AUA & EAU: Re-TURBT (EAU: within 4-6w).
AUA & EAU: Induction & maintenance BCG, 1-3y.
FOLLOW-UP
AUA: "Patient assessment every three months in the first two years after initial diagnosis followed by every six months for the subsequent two to three years, and then annually thereafter".
OR
OR
OR
EAU: Cystoscopy 3m post-TURBT, then 9m later if clear, then annually for 5y.
EAU: In-between follow-up, using cystoscopy & cytology, adapted to personal & subjective factors.
EAU: Cystoscopy & cytology 3m post-TURBT, then every 3m for 2y if clear, then every 6m until 5y, then annually.
Intuitively, the most cost-effective schedule. We suggest minimum 10y follow-up for all risk categories (see text).
UPPER TRACT SURVEILLANCE
AUA: "Surveillance often includes periodic upper tract imaging, especially for high-risk patients".
OR
EAU: Annual upper tract imaging with CTU or IVU for patients with high-risk tumors, or if cytology is positive in the absence of visible tumour.
Difficult to define a schedule for low- and intermediate-risk; CTU preferred (see text).
TREATMENT OF RECURRENCES
EAU: TURBT, although "fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden".
AUA: No definitive guidance.
We suggest biopsy before fulguration (see text).